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(54) Title: PHARMACEUTICAL COMBINATION OF BICALUTAMIDE AND TAMOXIFEN FOR PROVIDING AN ANTI-ANDROGENIC EFFECT AND AN ANTI-OESTROGENIC EFFECT

(57) Abstract: The present invention relates to a pharmaceutical product, daily dose or dose regimen comprising 4'-cyano- α' , α' -trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide (compound I) and tamoxifen. The product comprises compound I and tamoxifen in a ratio of 25 to 350:0.5 to 100 respectively. The invention also relates to a method of providing an anti-androgenic effect and an anti-oestrogenic effect in a patient, wherein the anti-oestrogenic effects is provided substantially without causing an additional increase in the levels of circulating androgens.

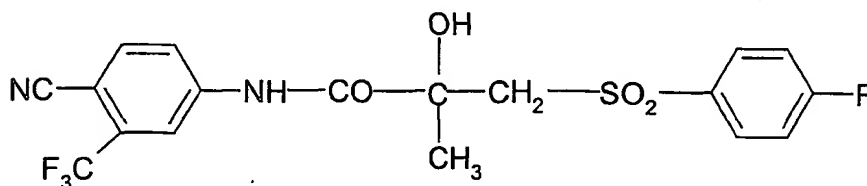
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Pharmaceutical combination of bicalutamide and tamoxifen for providing an anti-androgenic effect and an anti-oestrogenic effect.

The present invention relates to a pharmaceutical product, daily dose or dose regimen comprising 4'-cyano- α',α',α' -trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide and tamoxifen. The invention also relates to a method of
 5 providing an anti-androgenic effect and an anti-oestrogenic effect in a patient, wherein the anti-oestrogenic effect is provided substantially without causing an additional increase in the levels of circulating androgens. Furthermore, the invention relates to the use of 4'-cyano- α',α',α' -trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-
 10 toluidide and tamoxifen in the manufacture of a pharmaceutical product for this purpose.

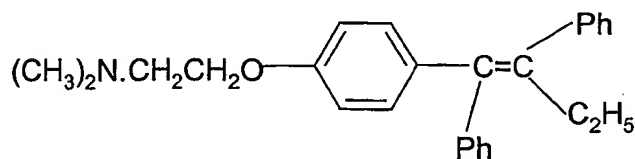
BACKGROUND TO THE INVENTION

15 Bicalutamide, a non-steroidal anti-androgen, is the racemate of 4'-cyano- α',α',α' -trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide and is known by the AstraZeneca trade name CASODEXTM. EP-100172 discloses 4'-cyano- α',α',α' -trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide (named in EP-100172 as 4-cyano-3-trifluoromethyl-*N*-(3-*p*-fluorophenylsulphonyl)-2-
 20 hydroxy-2-methylpropionyl)aniline) as the 8th compound listed in the table in Example 6. The corresponding structure is shown in formula I:-



4'-cyano- α',α',α' -trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide can exist in distinct R- and S- enantiomeric forms. The R-enantiomer is the (-) isomer and is the pharmacologically active compound *in vivo*. For further details of the enantiomers, reference is made to Tucker and Chesterton, J. Med. Chem. 31, pp 885-887
 5 (1988). EP-100172 provides a disclosure (without supporting examples) of a pharmaceutical composition comprising 4-cyano-3-trifluoromethyl-N-(3-*p*-fluorophenylsulphonyl-2-hydroxy-2-methylpropionyl)aniline in combination with "one or more drugs selected from anti-oestrogens, for example tamoxifen; aromatase inhibitors, for example testolactone or aminoglutethamide; progestins, for example medroxyprogesterone
 10 acetate; inhibitors of gonadotrophin secretion, for example danazol; LH-RH-analogues, for example buserelin; cytotoxic agents, for example cyclophosphamide; antibiotics, for example penicillin or oxytetracyclin; and anti-inflammatory agents, for example, especially for topical use, fluocinolone acetonide".

15 Tamoxifen, an anti-oestrogen, is known by the AstraZeneca trade name NOLVADEXTM. Tamoxifen is the trans isomer of 1-(*p*-beta-dimethylaminoethoxyphenyl)-1,2-diphenylbut-1-ene, which is disclosed in US-4,536,516. An alternative name is (Z)-2-[*p*-(1,2-diphenylbut-1-enyl)phenoxy]ethyl-dimethylamine. The corresponding structure is shown in formula II:-



II

Bicalutamide can be used for the treatment of prostate cancer in combination with an inhibitor of gonadotrophin secretion, for example a luteinising hormone releasing hormone
 25 (LHRH) agonist such as goserelin, buserelin, leuprorelin or triptorelin. The properties and usefulness of bicalutamide as an anti-androgen have been reviewed in B J A Furr *et al.*,

Urology, 1996, 47 (Suppl. 1A), 13-25, and G J C Kolvenbag *et al.*, Urology, 1996, 47 (Suppl. 1A), 70-79.

It has been observed that the administration of bicalutamide in single agent therapy to
5 humans causes an increase in the amount of testosterone circulating in the blood.
Blackledge *et al.*, (Urology, 1996, 47, Suppl. 1A), pp 44-47) discloses an approximate
doubling of the basal level of total testosterone. It is believed that such an increase in the
level of testosterone occurs when sufficient of the anti-androgen gains access to the CNS
and blocks androgen receptors in the hypothalamus. The consequential lack of feedback of
10 androgen causes additional release of LHRH by the hypothalamus which in turn causes
release of luteinising hormone (LH) and follicle stimulating hormone (FSH) by the
pituitary gland and production of testosterone in the testes. Aromatase enzyme in fat and
other tissues converts some of the increased concentration of testosterone to oestradiol,
which results in increased concentrations of oestrogen in the blood. Further discussion of
15 this is provided by C Mahler *et al.*, *Clinical Pharmacokinetics*, 1998, 34(5), pp 405-417.

A disadvantageous effect is produced. Namely, the increase in the levels of circulating
oestrogen may cause one or more of the side effects of gynaecomastia, breast tenderness,
hot flushes, impotence and reduction in libido. A discussion on gynaecomastia can be
20 found in C J Tyrrell, *Prostate Cancer and Prostatic Diseases*, 1999, 2(4): pp 167-171.

As explained above, the testosterone and LH levels tend to rise. Mahler *et al.* explain that
the rising oestrogen levels progressively activate the normal feedback mechanism, and so
the rise in LH and testosterone is limited. It is widely accepted in the art that oestrogen
25 levels are important in regulating LH secretion, and by this means testosterone secretion,
as invoked by Mahler *et al.* It is clear from numerous publications that the administration
of an anti-oestrogen to men and male animals reduces the negative feedback effect of
oestrogens on the hypothalamic-pituitary axis, thereby resulting in an increase in
luteinising hormone (LH) secretion. This in turn drives the testes to produce increased
30 quantities of testosterone. In this respect, reference is made to F H Comhaire *et al.*, *Human
Reproduction*, 1995, 10 (7), pp 1740-1744, where tamoxifen intake in adult men was
reported to increase testosterone and LH.

JJ Spijkstra *et al*, J. Clinical Endocrinology and Metabolism, 1988, 66(2), pp 355-360, reports a study of LH secretion in 13 normal men before and after the administration of tamoxifen for a 6 week period. An increase in mean serum testosterone, oestradiol, LH
5 levels, LH pulse frequency and LH pulse amplitude were observed after tamoxifen administration. Similar results were cited in men given the anti-oestrogen clomiphene citrate. Spijkstra *et al* suggest that the observed result with tamoxifen was due to an inhibition of negative feedback on pituitary oestrogen receptors.

10 DI Lewis-Jones *et al*, Andrologia 1987, 19(1): pp 86-90 reports that tamoxifen administration to men elevates the basal serum levels of LH, oestradiol "and particularly testosterone... The marked elevation in serum testosterone levels produced by the administration of tamoxifen may be a more successful method for elevating male hormone levels than the use of other pharmacological agents such as mesterolone".

15 L van Bergeijk *et al*, Horm. Metabol. Res., 1986, pp 558-564, reports that three months' treatment with tamoxifen in normogonadotrophic oligozoospermic men stimulated basal LH, FSH and testosterone levels. They suggested that oestrogens play a role in the negative feedback regulation of gonadotrophin release.

20 There is, therefore, a prejudice in the art against using an anti-oestrogen to combat the rise in oestrogen levels observed when an anti-androgen is administered to a male. This is because the anti-oestrogen would be expected, in view of the numerous previously reported studies, to produce a substantial additional increase in LH and testosterone, which
25 in turn would be expected to compromise the anti-androgenic effect of the anti-androgen.

There is therefore a need for a treatment that can provide an anti-androgenic effect and combat the rise in oestrogen levels, thereby suppressing a side effect selected from gynaecomastia, breast tenderness, hot flushes, impotence and reduction in libido, without

substantially causing an additional increase in the levels of circulating androgens above the levels produced by the anti-androgen alone.

5 SUMMARY OF THE INVENTION

The present invention fulfils this need by providing a pharmaceutical product for administration to a patient for providing an anti-androgenic effect and an anti-oestrogenic effect in the patient, the product comprising a compound of formula I or a
10 pharmaceutically acceptable salt or solvate thereof and tamoxifen or a pharmaceutically acceptable salt or solvate thereof, wherein the compound of formula I and tamoxifen are provided in a ratio of 25 to 350 : 0.5 to 100 respectively. The tamoxifen is optionally used in its citrate form.

15 As a result of the present invention, the anti-oestrogenic effect is provided substantially without causing an additional increase in the levels of circulating androgens. By this, we mean that the androgen levels (eg, as indicated by total or free testosterone in blood) in the patient do not substantially increase above the level usually observed when the anti-androgen alone is administered to patients.

20 The present invention also provides a daily pharmaceutical dose for administration to a patient for providing an anti-androgenic effect and an anti-oestrogenic effect in the patient, the dose comprising a compound of formula I or a pharmaceutically acceptable salt or solvate thereof and from 0.5 to 100 mg of tamoxifen or a pharmaceutically acceptable salt
25 or solvate thereof.

In addition, the present invention provides a dose regimen for such purpose comprising a compound of formula I or a pharmaceutically acceptable salt or solvate thereof (eg, 150 mg thereof) and from 0.5 to 100 mg of tamoxifen or a pharmaceutically acceptable salt or

solvate thereof for simultaneous or sequential administration to the patient.

In another aspect, the present invention provides a pharmaceutical product for administration to a patient for providing an anti-androgenic effect and an anti-oestrogenic effect in the patient, the product comprising a compound of formula I or a pharmaceutically acceptable salt or solvate thereof and tamoxifen citrate.

Other aspects of the invention relate to the use in the manufacture of a pharmaceutical product of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof and tamoxifen or a pharmaceutically acceptable salt or solvate thereof for simultaneous or sequential administration to a patient, for:-

(a) providing an anti-androgenic effect and an anti-oestrogenic effect in the patient, wherein the anti-oestrogenic effect is provided substantially without causing an additional increase in the levels of circulating androgens; or

(b) providing an anti-androgenic effect in the patient and suppressing increase in the incidence or severity of a side effect selected from gynaecomastia, breast tenderness, hot flushes, impotence and reduction in libido, substantially without causing an additional increase in the levels of circulating androgens.

By "suppressing increase in the incidence or severity of a side effect", we mean providing a lower incidence or severity compared with the side effect produced when the anti-androgen is administered alone, or eliminating the side effect.

The present invention further provides a method of providing an anti-androgenic effect in a patient comprising simultaneously or sequentially administering a compound of formula I or a pharmaceutically acceptable salt or solvate thereof and tamoxifen or a pharmaceutically acceptable salt or solvate thereof to the patient, wherein the method

further provides an anti-oestrogenic effect in the patient substantially without causing an additional increase in the levels of circulating androgens.

5 DETAILED DESCRIPTION OF THE INVENTION

We have now surprisingly found that both an anti-androgenic effect and an anti-oestrogenic effect can be produced in a patient, wherein the anti-oestrogenic effect is provided substantially without causing an additional increase in the levels of circulating
10 androgens. This is achieved by administering to the patient a product comprising a compound of formula I or a pharmaceutically acceptable salt or solvate thereof and tamoxifen or a pharmaceutically acceptable salt or solvate thereof, wherein the compound of formula I and tamoxifen are provided in a ratio respectively of 25 to 350 (preferably the lower end of the range being 50; preferably the upper end of the range being 300, 150 or
15 50; suitable values in the ranges being 150 or 50) : 0.5 to 100 (preferably the lower end of the range being 1 or 5; preferably the upper end of the range being 40, 20 or 10; a suitable value in the range being 20). The term "product" is intended to mean either a mixture of the compound of formula I and tamoxifen (eg, provided as a capsule or tablet containing both compounds) or a kit comprising separate amounts of the compounds (eg, a set of
20 tamoxifen tablets and a separate set of tablets of the other compound). The latter product can be used for simultaneous or sequential (ie, temporally spaced) administration of the compounds to the patient, while the pre-mixed compounds are for simultaneous administration. Factors such as the rate of absorption, metabolism and the rate of excretion of each agent will affect their presence at the tumour site. Such factors are routinely
25 considered by, and are well within the ordinary skill of, the clinician when he contemplates the treatment of a medical condition which requires the conjoint administration of two agents in order to obtain a beneficial effect.

The compound of formula I is included to provide an anti-androgenic effect, in that this
30 compound blocks androgen activity. The tamoxifen is included to provide an anti-oestrogenic effect, in that this compound prevents oestrogen activity.

The anti-androgenic effect is useful for treating cancer, for example prostate cancer. Particular examples are advanced prostate cancer and early prostate cancer. The anti-androgenic effect may be useful for prophylaxis, in order to reduce the risk of prostate cancer occurrence in patients. This could be especially useful in men genetically pre-disposed to prostate cancer. Conventional methods are available to classify patients according to their risk of contracting prostate cancer, for example by assessment of family history and measurements over time of particular blood proteins such as prostate specific antigen (PSA). Other uses for the anti-androgenic effect are the treatment of a non-malignant disease of the prostate gland (eg, benign prostatic hyperplasia or hypertrophy) and acne.

The anti-oestrogenic effect is useful for suppressing increase in the incidence or severity of a side effect selected from gynaecomastia, breast tenderness, hot flushes, impotence, reduction in libido, nausea, vomiting, fatigue and diarrhoea. Such side effects have been observed with monotherapy use of anti-androgens. Preferably, the side effect is one or both of gynaecomastia and breast tenderness.

A suitable dose regimen or daily pharmaceutical dose comprises the compound of formula I or a pharmaceutically acceptable salt or solvate thereof and from 0.5 to 100 mg of tamoxifen or a pharmaceutically acceptable salt or solvate thereof. Preferably, for tamoxifen the lower end of the range is 1 or 5 mg; preferably the upper end of the range is 40, 20 or 10 mg; a suitable value in the range being 20 mg. The dose or the regimen preferably comprises from 25 to 350 mg of the compound of formula I or a pharmaceutically acceptable salt or solvate thereof. Preferably the lower end of the range is 50 mg; preferably the upper end of the range is 300, 150 or 50 mg; suitable values in the ranges are 150 or 50 mg.

For the regimen, each compound is preferably administered daily. Another possible regime would be dosing of the compound of formula I on alternate days and dosing of the tamoxifen also on (the same or different) alternate days. To this end, the regimen may include administration instructions. Preferably, a dose of the compound of formula I is
5 administered every 3, 4, 5, 6 or 7 days and the tamoxifen is administered every 3, 4, 5, 6 or 7 days (eg, on the same day as the compound of formula I).

In one embodiment of the present invention, the compound of formula I consists of 90 to 100% of the R-enantiomer and 10 to 0% of the S-enantiomer thereof. In a preferred
10 embodiment, 100% of the R-enantiomer is used.

In another embodiment, the compound of formula I consists of a racemic mixture of the R- and S-enantiomers thereof.

15 The patient can be a human male, eg an adult, but the treatment of other mammals (except rats) is also contemplated.

The products, doses and regimens of the invention may be in a form suitable for oral use (for example as tablets, capsules, aqueous or oily suspensions, emulsions or dispersible
20 powders or granules), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions; for example for use within a transdermal patch), for parenteral administration (for example as a sterile aqueous or oily solution or suspension for intravenous, subcutaneous, intramuscular or intravascular dosing), or as a suppository for rectal dosing. Preferably the compositions of the invention are in a form suitable for
25 oral use, for example as tablets or capsules.

The products, doses and regimens of the invention may be obtained by conventional procedures using conventional pharmaceutically-acceptable diluents or carriers that are well known in the art.

Suitable pharmaceutically-acceptable diluents or carriers for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or alginic acid; binding agents such as gelatin or starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

When we mention providing an anti-oestrogenic effect without causing an additional increase in the levels of circulating androgens, we mean that the androgen levels (eg, as indicated by total or free testosterone in blood) in the patient do not substantially increase above the maximum level usually observed when the anti-androgen alone is administered to patients. An enabling illustration is provided in the human clinical trial below.

HUMAN CLINICAL TRIAL

The following clinical trial was performed to determine the effect of the administration of CASODEX™ together with NOLVADEX™ on free testosterone levels in healthy male volunteers over a 6 week period.

Protocol

Key Inclusion Criteria: Male, aged 65 years or above showing no clinically significant abnormalities in routine haematological and biochemical tests and having endocrinology
5 and prostate specific antigen (PSA) results within normal limits.

Key Exclusion Criteria: Previous inclusion in a clinical trial using CASODEX™;
concurrent treatment with any drugs with the exception of paracetamol; history or presence
of any testicular abnormality; history or presence of gastrointestinal, hepatic or renal
10 disease, or other condition known to interfere with the absorption, distribution, metabolism
or excretion of drugs; a clinically significant illness within 2 weeks of trial
commencement; definite or suspected personal or family history of significant adverse
drug reactions or any hypersensitivity to CASODEX™ or NOLVADEX™; treatment within
the previous 3 months with any drugs known to have a well-defined potential for
15 hepatotoxicity or hepatic interaction.

Dosage: The CASODEX™ was administered daily at a dose of 150 mg and the
NOLVADEX™ was administered daily at a dose of 20 mg. All treatments were in tablet
form and taken once daily. Daily treatment with CASODEX™ plus NOLVADEX™ was for
20 6 weeks, this period being selected as the minimum time to attain steady-state plasma
concentrations for the drugs. Another set of volunteers were administered CASODEX™
alone at a daily dose of 150 mg for 4 weeks. All treatments were in tablet form and taken
once daily.

25

Key Assessment: Free testosterone concentrations were measured during the course of
the trial.

Results

Summaries of the free testosterone concentrations over the treatment periods are presented in Table 1 (for CASODEX™ in combination with NOLVADEX™) and Table 2 for
 5 CASODEX™ alone.

Table 1 Free testosterone concentrations following treatment with CASODEX™ plus NOLVADEX™

Parameter	Day 1	Day 8	Day 22	Day 43	Follow-up
Testosterone (nmol/l)					
n	7	7	7	7	7
gmean	0.045	0.059	0.077	0.063	0.056
CV	11.970	18.628	34.582	34.303	22.686
Minimum	0.04 - 0.05	0.05 - 0.08	0.04 - 0.10	0.04 - 0.09	0.04 - 0.07
Ratio to Day 1	-	1.30	1.69	1.38	1.23

10 CV=Coefficient of variation gmean=Geometric mean n=Number of observations

Day 1 samples were drawn before dosing, and therefore act as a baseline measurement.

No volunteers in the CASODEX™ plus NOLVADEX™ group experienced gynaecomastia.

Table 2 Free testosterone concentrations following treatment with CASODEXTM alone

Parameter	Day 1	Day 29
Testosterone (nmol/l)		
n	7	7
gmean	0.048	0.076
CV	30.415	26.219
Minimum	0.03 - 0.07	0.00 - 0.12
Ratio to Day 1	-	1.58
CV=Coefficient of variation gmean=Geometric mean n=Number of observations		

5 Day 1 samples were drawn before dosing, and therefore act as a baseline measurement.

Conclusion

When CASODEXTM alone was administered, the mean free testosterone concentration
 10 increased 58% by the end of the treatment period. With continued administration of
 CASODEXTM beyond the 4th week, this figure would be expected to rise (corresponding to
 an approximate doubling of the mean total testosterone concentration). In this respect,
 reference is made to a trial reported by Verhelst, J *et al* ("Endocrine profiles during
 administration of the new non-steroidal anti-androgen Casodex in prostate cancer",
 15 Verhelst, J *et al*, Clin. Endocrinol. (Oxf) 1994, Oct., 41(4), pp 525-30), which reported an
 increase of 57% in the mean free testosterone concentration after 24 weeks of daily
 administration of 150 mg CASODEXTM alone.

Reference to Table 1 shows that the co-administration of NOLVADEXTM with
 20 CASODEXTM produced no additional clinically significant change in the mean
 concentration of free testosterone. Indeed, by the end of the treatment period the increase
 in the mean concentration was 38%.

The results therefore support our surprising finding that in the present invention the tamoxifen does not compromise the anti-androgenic effect of the anti-androgen of formula I, in that contrary to the expectations of the skilled person based on the aforementioned prejudice in the art, the use of the tamoxifen does not cause an additional increase in the
5 levels of androgens beyond the levels expected when anti-androgen alone is used.

CLAIMS

1. A pharmaceutical product for administration to a patient for providing an anti-androgenic effect and an anti-oestrogenic effect in the patient, the product comprising a compound of formula I or a pharmaceutically acceptable salt or solvate thereof and tamoxifen or a pharmaceutically acceptable salt or solvate thereof, wherein the compound of formula I and tamoxifen are provided in a ratio of 25 to 350 : 0.5 to 100 respectively.
2. A daily pharmaceutical dose for administration to a patient for providing an anti-androgenic effect and an anti-oestrogenic effect in the patient, the dose comprising a compound of formula I or a pharmaceutically acceptable salt or solvate thereof and from 0.5 to 100 mg of tamoxifen or a pharmaceutically acceptable salt or solvate thereof.
3. A dose regimen for providing an anti-androgenic effect and an anti-oestrogenic effect in a patient, the regimen comprising a compound of formula I or a pharmaceutically acceptable salt or solvate thereof and from 0.5 to 100 mg of tamoxifen or a pharmaceutically acceptable salt or solvate thereof for simultaneous or sequential administration to the patient.
4. The dose of claim 2, or the regimen of claim 3, comprising from 25 to 350 mg of the compound of formula I or a pharmaceutically acceptable salt or solvate thereof.
5. A dose regimen for providing an anti-androgenic effect and an anti-oestrogenic effect in a patient, the regimen comprising 150 mg a compound of formula I or a pharmaceutically acceptable salt or solvate thereof and from 0.5 to 100 mg of tamoxifen or a pharmaceutically acceptable salt or solvate thereof for simultaneous or sequential administration to the patient.

6. A pharmaceutical product for administration to a patient for providing an anti-androgenic effect and an anti-oestrogenic effect in the patient, the product comprising a compound of formula I or a pharmaceutically acceptable salt or solvate thereof and tamoxifen citrate.
- 5
7. Use in the manufacture of a pharmaceutical product of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof and tamoxifen or a pharmaceutically acceptable salt or solvate thereof for simultaneous or sequential administration to a patient, for providing an anti-androgenic effect and an anti-oestrogenic effect in the patient, wherein the anti-oestrogenic effect is provided
- 10 substantially without causing an additional increase in the levels of circulating androgens.
8. Use in the manufacture of a pharmaceutical product of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof and tamoxifen or a pharmaceutically acceptable salt or solvate thereof for simultaneous or sequential administration to a patient, for providing an anti-androgenic effect in the patient and suppressing increase in the incidence or severity of at least one side effect selected from gynaecomastia, breast tenderness, hot flushes, impotence and reduction in libido,
- 15 substantially without causing an additional increase in the levels of circulating androgens.
- 20
9. A method of providing an anti-androgenic effect in a patient comprising simultaneously or sequentially administering a compound of formula I or a pharmaceutically acceptable salt or solvate thereof and tamoxifen or a pharmaceutically acceptable salt or solvate thereof to the patient, wherein the method
- 25 further provides an anti-oestrogenic effect in the patient substantially without causing an additional increase in the levels of circulating androgens.

10. The product, dose, regimen, use or method of any preceding claim, wherein the compound of formula I consists of 90 to 100% of the R-enantiomer and 10 to 0% of the S-enantiomer thereof.
- 5 11. The product, dose, regimen, use or method of any one of claims 1 to 9, wherein the compound of formula I consists of a racemic mixture of the R- and S-enantiomers thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/01162

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/277, A61K 31/165, A61P 5/28, A61P 5/32
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM.ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4895715 A (RUDOLPH NERI ET AL), 23 January 1990 (23.01.90), the abstract; column 3, line 12 - column 4, line 15; the claims --	1-11
A	UROLOGY, Volume 54, No 6A, 1999, Jerome P. Richie, m.d., "Anti-androgens and other hormonal therapies for prostate cancer" page 15 - page 18 --	1-11
A	Journal of Cancer Research Clinical Oncology, Volume 119, 1993, A. Maucher et al, "Antiproliferative activity of casodex (ICI 176.334) in hormone-dependent tumours" page 669 - page 674 --	1-11

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

20 Sept 2001

Date of mailing of the international search report

21 -09- 2001

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/01162

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0100172 A1 (IMPERIAL CHEMICAL INDUSTRIES PLC), 8 February 1984 (08.02.84), page 14, line 1 - line 11; page 27, 8th compound in table; the claims --	1-11
A	WO 9519770 A1 (SEPRACOR, INC.), 27 July 1995 (27.07.95) --	1-11
A	US 4536516 A (MICHAEL J.K. HARPER ET AL), 20 August 1985 (20.08.85) -- -----	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01162**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 2-5, 7-9, 10 (partly), 11 (partly)
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☒ Claims Nos.: 1-11
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The wording "a compound of formula I" is not clear and concise. Confer PCT, Article 6 and Rule 6.2(a). The search is based on the compound of formula I specified in the description page 1, line 15 - page 2, line 5.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

With the present wording claims 2-5, 7-9, 10 (partly), 11, (partly) relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/09/01

International application No.

PCT/SE 01/01162

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INTERNATIONAL SEARCH REPORT
Information on patent family members

03/09/01

International application No.

PCT/SE 01/01162

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